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EXAMINER

NGUYEN, QUANG

ART UNIT PAPER NUMBER

1633

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.

09/316,199

Applicant(s)

MCCLUSKIE ET AL.

Examiner

Quang Nguyen, Ph.D.

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 May 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-9,11-13,15-23,25-28,126-129,131 and 133-136 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-9,11-13,15-23,25-28,126-129,131 and 133-136 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/3/05; 3/7/05</u> | 6) <input type="checkbox"/> Other: _____ |

50-2

DETAILED ACTION

This application has been transferred to examiner Quang Nguyen, Ph.D. in GAU 1633.

Amended claims 1, 4-9, 11-13, 15-23, 25-28, 126-129, 131 and 133-136 are pending in the present application.

Response to Amendment

The rejection under 35 USC 102(e) as being anticipated by Hutcherson (US 6,727,230 B1) or Agrawal (US 6,526,334) is withdrawn in light of Applicants' amendment.

The rejections under 35 USC 103(a) as being unpatentable over Briles et al. (US 6,042,838) in view of various references are withdrawn in light of Applicants' amendment.

Claim Objections

Claim 9 is objected to because the species "derivatives of cholera toxin" is recited twice in the Markush group. Additionally, the terms "MLP", "MDP", "MF59", "SAF", "PROVAX", "PCPP" and "ISCOMS" should be spelled out in full at the first occurrence of the terms.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 131 and 133-134 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection.***

Amended claim 131 recites "and wherein the oligonucleotide is administered to a mucosal surface different from that at which the subject is exposed to the antigen". It is noted that the term "exposed to" refer to either the active step of contacting the subject with an antigen or the passive exposure of the subject to the antigen *in vivo* (see specification page 27, lines 14-16). There is literally no support in the originally filed specification for a method for inducing a mucosal immune response in a subject in which the oligonucleotide is administered to a mucosal surface different from that at which the subject is exposed to the antigen. In the amendment filed on 1/28/02, Applicants cited page 5, lines 17-24 as an alleged support for this claimed embodiment. However, the cited passage merely states that the method involves the steps of orally, intranasally, ocularly, vaginally, or rectally administering to a subject an effective amount for inducing an immune response of an oligonucleotide of the present invention and exposing the subject to an antigen to induce the immune response, and in some embodiments the antigen is administered orally, intranasally, ocularly, vaginally, or

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rectally. This cited passage does not provide a written support for the specific method step in which the oligonucleotide is administered to a mucosal surface different from that at which the subject is exposed passively or actively to the antigen, and particularly the concept for a method in which the oligonucleotide is administered to a mucosal surface different from that at which the subject is administered the antigen. Throughout the specification, Applicants teach that both the oligonucleotide and the antigen are administered orally, intranasally, ocularly, vaginally or rectally to a mucosal surface (see at least examples 1-5).

Therefore, given the lack of guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of the claimed invention at the time the application was filed.

Should Applicants overcome the above New Matter rejection, claims 131 and 133-134 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This is a new ground of rejection.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

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Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

When read in light of the specification, the sole purpose for a method of inducing a mucosal immune response in a subject as claimed is to attain prophylactic and/or therapeutic effects. There is no other disclosed use for the induction of a mucosal immune response in a subject. As enablement requires the specification to teach how to make and use the claimed invention, the instant specification is not enabled for the method as claimed for the following reasons.

1. *The breadth of the claims*

The claims are drawn to a method for inducing a mucosal immune response comprising administering to any mucosal surface of any subject in need of a mucosal immune response an effective amount for inducing a mucosal immune response of an oligonucleotide 8 to 100 nucleotides in length, having a sequence including at least the following formula: 5'-X1X2CGX3X4-3' wherein C is unmethylated, wherein X1, X2, X3, and X4 are nucleotides, and exposing the subject to any antigen, to induce the mucosal immune response wherein the antigen is not encoded in a nucleic acid vector and wherein the oligonucleotide is administered to a mucosal surface different from that at which the subject is exposed either passively or actively to the antigen.

2. *The state and the unpredictability of the prior art*

At about the effective filing date of the present application (5/22/98), little was known whether a CpG motif containing oligonucleotide is capable of inducing a therapeutic mucosal immune response by itself in a subject against any antigen that the

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subject is exposed to, particularly the subject is exposed to the antigen at a mucosal surface that is different from that at which the CpG oligonucleotide is administered. Numerous post-filing publications after the effective filing date of the present application still only teach that CpG oligonucleotide is an effective mucosal adjuvant in mice when co-administered with protein antigens as evidenced by the teachings of Moldoveanu et al. (Vaccine 16:1216-1224, 1998; IDS), Davis et al. (J. Immunology 160:870-876, 1998; IDS), McCluskie et al. (J. Immunology 161:4463-4466, 1998; IDS); McCluskie et al. (Current Opinion in Invest. Drugs 2:35-39; 2001; IDS) and McCluskie et al. (Critical Reviews in Immunology 21:103-120, 2001; IDS). With respect to DNA vaccines containing a CpG motif, McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999; Cited previously) have noted that the route of administration and DNA doses as well as numerous other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types of host immune responses elicited (page 313, see the section titled "Role of CpG immunostimulatory sequences). Additionally, Caufield (WO 98/52962) also already demonstrated the lack of an adjuvant effect in a situation where a CpG containing oligonucleotide was injected in the opposite leg from where the antigen was injected (see example 5 on pages 25-26).

3. The amount of direction or guidance provided

The instant specification fails to provide sufficient guidance for a skilled artisan in the art on how to obtain any therapeutic mucosal immune response against any antigen in any subject, wherein the subject is exposed either passively or actively to the antigen

at a different mucosal surface from which the CpG oligonucleotide is administered. There is no evidence in the prior art at the effective filing date of the present application or in the instant disclosure demonstrate that a CpG motif containing oligonucleotide by itself is capable of inducing an effective antigen-specific mucosal immune response that yields prophylactic and/or therapeutic effects in a subject against any antigen that the subject is exposed to. Nor is there any evidence of record indicating or suggesting that a CpG oligonucleotide has an effective adjuvant effect for any antigen that is not co-administered or administered at the same site (including a mucosal surface) as that of the CpG oligonucleotide. As already noted above, Caufield (WO 98/52962) already demonstrated the lack of an adjuvant effect in a situation where a CpG containing oligonucleotide was injected in the opposite leg from where the antigen was injected (see example 5 on pages 25-26). In addition, the instant specification teaches explicitly that CpG alone did not induce IgA in lung washes, however it induced IgA in the feces but only in some animals (see page 63, lines 20-29), and there is no evidence that the detectable IgA is effective to yield any prophylactic and/or therapeutic effects that are contemplated by Applicants. Even several years after the effective filing date of the present application, McCluskie et al. (Current Opinion in Invest. Drugs 2:35-39; 2001; IDS) still state "[w]e and others have recently shown CpG DNA to be an effective mucosal adjuvant in mice when co-administered with protein antigens" (page 35, col. 2, bottom of second paragraph). It is further noted that the physiological art is recognized as unpredictable (MPEP 2164.03).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the relevant art for the attainment of a therapeutic mucosal immune response against any antigen in any subject, wherein the subject is exposed either passively or actively to the antigen at a different mucosal surface from which the CpG oligonucleotide is administered, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the methods as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 22 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

Regarding claim 9, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Accordingly, the metes and bounds of the claim are not clearly determined.

Claim 22 is vague and indefinite in that the metes and bounds of the term "derived from" are unclear. It is unclear the nature and number of steps required to obtain a derivative of an antigen. The term implies a number of different steps that may or may not result in a change in the functional characteristics of an antigen from the source that it is "derived from". It would be remedial to amend the claim language to

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use the term - - obtained from - -, which implies a more direct method of acquiring the antigen.

Claim 26 recites the limitation "the mucosal immunity" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. In claim 1 which claim 26 is dependent, there is no recitation of any mucosal immunity. Which mucosal immunity do Applicants refer to? Clarification is requested because the metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4-9, 11-13, 15-23, 26-28, 126-129 and 135-136 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieg (US 6,218,371; Cited previously) as evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously). ***This is a new ground of rejection.***

Krieg discloses a method of stimulating an immune response in a subject, said method comprises administering to the subject exposed to an antigen an effective amount for inducing a synergistic antigen specific immune response of an

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immunopotentiating cytokine (e.g., GM-CSF, IL-2, IL-4 and IFN-gamma, a non-oligonucleotide mucosal adjuvant), and an immunostimulatory CpG oligonucleotide having a sequence including at least the following formula: X1CGX2 wherein the oligonucleotide includes at least 8 nucleotides wherein C is unmethylated and wherein X1 and X2 are nucleotides, and wherein an antigen is optionally administered to the subject in conjunction with the immunostimulatory CpG oligonucleotide and the immunopotentiating cytokine (See Summary of the Invention, and particularly claim 6). Krieg also teaches that the antigen may be any type of antigen known in the art, for example, a tumor antigen, a viral antigen, a microbial antigen and an allergen (col. 3, lines 27-30; at least cols. 9-15), and that the subject is passively exposed to the antigen or the subject has or is at risk of having a viral infection or a tumor or an allergy including asthma (co. 3, lines 30-38; col. 4, lines 4-10; col.10, line 66 continues to line 28 of col. 12). Krieg further discloses that an antigen and/or CpG oligonucleotide/immunopotentiating cytokine is administered directly to the subject by any means such as oral, mucosal, nasal, rectal, intranasal, intratracheal, intravenous, intramuscular or subcutaneous administration (col. 18, lines 47-52; col. 26, lines 40-50; col. 31, lines 57-63) alone or with colloidal dispersion systems that include macromolecular complexes, nanocapsules, microspheres, beads, lipid-based systems including oil-in-water emulsions, micelles, mixed micelles and liposomes (col. 19, lines 36-67). The CpG motif containing oligonucleotides including 5'-GTCpGTT-3' containing oligonucleotides are disclosed in column 23. The CpG oligonucleotides are stabilized by incorporating a phosphate backbone modification, for example a phosphorothioate or

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phosphorodithioate modification at the 5' end or 3' end or both ends of the oligonucleotides (col. 23, lines 37-48). Krieg also teaches that a second antigen which may be the same or different from the first antigen may be administered to the subject at some time point after the administration of CpG and immunopotentiating cytokine in the presence or absence of additional CpG (a boost) and cytokine (col. 26, lines 15-19).

In view of the factual evidence established by McCluskie et al which shows that oligonucleotides containing CpG motifs can induce an antigen-specific mucosal immune response in a subject upon oral, intrarectal or intranasal delivery of an antigen together with the CpG oligonucleotides (see at least Figure 2); the methods taught by Krieg would inherently generate an induced mucosal immune response in the treated subject via mucosal routes such as oral, mucosal, nasal, rectal, intranasal administrations, particularly in view of the absence of evidence to the contrary.

Response to Arguments

Applicant's argument related in part to the above rejection in the Amendment filed on 5/4/05 (page 9) has been fully considered, but it is not found persuasive. Applicants relied mainly on the Declaration from Inventor Heather L. Davis in an attempt to remove Krieg (US 6,218,371) as a prior art reference.

The Declaration filed on 11/24/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the Krieg reference (US 6,218,371). The Krieg reference is a U.S. patent or U.S. patent application publication of a pending or patented application that claims the rejected invention (see claim 6 of the issued US patent). An affidavit or

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declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention, see MPEP § 2306. If the reference and this application are not commonly owned, the reference can only be overcome by establishing priority of invention through interference proceedings. See MPEP Chapter 2300 for information on initiating interference proceedings. If the reference and this application are commonly owned, the reference may be disqualified as prior art by an affidavit or declaration under 37 CFR 1.130. See MPEP § 718.

Accordingly, claims 1, 4-9, 11-13, 15-23, 26-28, 126-129 and 135-136 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieg (US 6,218,371) as evidenced by McCluskie et al. (Vaccine 19:413-422, 2001) for the reasons set forth above.

Claims 1, 4, 8-9, 11-13, 15-23, 26 and 135-136 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieg et al. (US 6,239,116; Cited previously) as evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously). ***This is a new ground of rejection.***

Krieg et al disclose a method of stimulating immune activation by administering an isolated immunostimulatory nucleic acid sequence containing a CpG motif represented by the formula: 5'-N1X1CpGX2N2-3', wherein at least one nucleotide separates consecutive CpGs; X1 is adenine, guanine, or thymine; X2 is cytosine or thymine; N is any nucleotide and N1+N2 is from about 0-26 bases with the proviso that N1 and N2 do not contain a CCGG quadmer or more than one CCG or CGG trimer; and

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the nucleic acid sequence is from about 8-30 bases in length and wherein the immune activation effects predominantly a Th1 pattern of immune activation (see Summary of the Invention). Krieg et al. further teach that the nucleic acid sequence can be administered to stimulate a subject's response to a vaccine to ameliorate disorders such as cancer, viral, fungal, bacterial or parasitic infection, specifically the nucleic acid sequence can be administered to a subject in conjunction with a particular allergen as a type of desensitization therapy to treat the occurrence of an allergic reaction associated with an asthmatic disorder (col. 6, line 63 continues to line 7 of col. 7). Infectious virus, bacteria, fungi are listed in columns 10-11. The CpG oligonucleotides are stabilized by incorporating a phosphate backbone modification, for example a phosphorothioate or phosphorodithioate modification at the 5' end or 3' end (col. 14, lines 3-32). Krieg et al. also specifically teach the sequence 1826 having the sequence TCCATGACGTTCTGACGTT is a strong immune activating sequence and is a superb adjuvant, with efficacy comparable or superior to complete Freund's, but without apparent toxicity, (col. 22, lines 54-62). Krieg et al. further teach that the immunostimulatory nucleic acid sequence can be administered to a subject slightly before or at the same time as the vaccine, and that a conventional adjuvant (e.g., aluminum precipitates) may optionally be administered in conjunction with the vaccine, which is minimally comprised of an antigen, as the conventional adjuvant may further improve the vaccination by enhancing antigen absorption (col. 45, lines 37-46). Routes of administering the immunostimulatory nucleic acid include oral and transdermal and others (col. 46, lines 55-64). It is also noted that a subject having an immune system

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deficiency such as a subject having a cancer or an infection is a subject in need of at least a mucosal immune response.

In view of the factual evidence established by McCluskie et al which shows that oligonucleotides containing CpG motifs can induce an antigen-specific mucosal immune response in a subject upon oral, intrarectal or intranasal delivery of an antigen together with the CpG oligonucleotides (see at least Figure 2); the methods taught by Krieg would inherently generate an induced mucosal immune response in the treated subject via the oral delivery of the immunostimulatory nucleic acid in conjunction with an antigen vaccine (e.g., an allergen, tumor, viral), particularly in view of the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg (US 6,218,371; Cited previously) in view of Craig (US 6,689,757; Cited previously) as evidenced by McCluskie et al. (Vaccine 19:413-422, 2001; Cited previously). ***This is a new ground of rejection.***

Krieg discloses a method of stimulating an immune response in a subject, said method comprises administering to the subject exposed to an antigen an effective amount for inducing a synergistic antigen specific immune response of an immunopotentiating cytokine (e.g., GM-CSF, IL-2, IL-4 and IFN-gamma, a non-oligonucleotide mucosal adjuvant), and an immunostimulatory CpG oligonucleotide having a sequence including at least the following formula: X1CGX2 wherein the oligonucleotide includes at least 8 nucleotides wherein C is unmethylated and wherein X1 and X2 are nucleotides, and wherein an antigen is optionally administered to the subject in conjunction with the immunostimulatory CpG oligonucleotide and the immunopotentiating cytokine (See Summary of the Invention, and particularly claim 6). Krieg also teaches that the antigen may be any type of antigen known in the art, for example, a tumor antigen, a viral antigen, a microbial antigen and an allergen (col. 3, lines 27-30; at least cols. 9-15), and that the subject is passively exposed to the antigen or the subject has or is at risk of having a viral infection or a tumor or an allergy including asthma (co. 3, lines 30-38; col. 4, lines 4-10; col.10, line 66 continues to line 28 of col. 12). Krieg further discloses that an antigen and/or CpG

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oligonucleotide/immunopotentiating cytokine is administered directly to the subject by any means such as oral, mucosal, nasal, rectal, intranasal, intratracheal, intravenous, intramuscular or subcutaneous administration (col. 18, lines 47-52; col. 26, lines 40-50; col. 31, lines 57-63) alone or with colloidal dispersion systems that include macromolecular complexes, nanocapsules, microspheres, beads, lipid-based systems including oil-in-water emulsions, micelles, mixed micelles and liposomes (col. 19, lines 36-67). The CpG motif containing oligonucleotides including 5'-GTCpGTT-3' containing oligonucleotides are disclosed in column 23. The CpG oligonucleotides are stabilized by incorporating a phosphate backbone modification, for example a phosphorothioate or phosphorodithioate modification at the 5' end or 3' end or both ends of the oligonucleotides (col. 23, lines 37-48). Krieg also teaches that a second antigen which may be the same or different from the first antigen may be administered to the subject at some time point after the administration of CpG and immunopotentiating cytokine in the presence or absence of additional CpG (a boost) and cytokine (col. 26, lines 15-19).

In view of the factual evidence established by McCluskie et al which shows that oligonucleotides containing CpG motifs can induce an antigen-specific mucosal immune response in a subject upon oral, intrarectal or intranasal delivery of an antigen together with the CpG oligonucleotides (see at least Figure 2); the methods taught by Krieg would generate an induced mucosal immune response in the treated subject via mucosal routes such as oral, mucosal, nasal, rectal, intranasal administrations.

However, Krieg does not teach a method further comprising administering a B-7 costimulatory molecule.

At the effective filing date of the present application, Craig already teach methods for vaccinating a mammal against a disease using additional factors that include cytokines and/or co-stimulatory molecules such as B7-1, B7-2, ICAM-1 and ICAM-3 in conjunction with a nucleic acid and antigen (col. 6, lines 35-49).

It would have been obvious for an ordinary skilled to further employ a co-stimulatory molecule such as B7-1, B7-2 in the method taught by Krieg in light of the teachings of Craig.

An ordinary skilled artisan would have been motivated to carry out the above modification because the further administration of co-stimulatory molecules such as B7-1 and B7-2 as in the case of cytokines would further enhance the induced immune response in the subject.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Krieg and Craig, coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 4-6, 8-9, 11-12, 15-23, 26-28, 126-129, 135 and 136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morein et al. (U.S. 6,607,732) in view of Krieg et al. (US 6,239,116; Cited previously). ***This is a new ground of rejection.***

Morein et al teach a method of eliciting an immune response in a subject comprising administering to a mucosal organ of a subject an effective amount of an

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immunogenic composition for eliciting an immune response comprising an immunostimulating complex in the form of ISCOM matrix containing at least one glycoside, at least one lipid of which one being cholesterol, at least one mucus targeting molecule (e.g., bacterial cholera toxin, heat-labile toxin, envelope proteins from viruses, proteins from bacteria) and at least one passenger antigen chosen from pharmacological immuno-affecting or enhancing or immunogenic substances that do not easily reach lymphatic tissue through mucous membranes (e.g., gB and gD from various Herpes viruses, envelope protein in retroviruses, hepadna viruses, bacteria), vaccines and immunostimulating agents by oral, nasal (intranasal), urogenital and/or rectal administration (see Summary of the Invention, col. 4, line 54 continues to line 48 of col. 5; examples, and the claims). Morein et al further teach that rise in total antibody titres was obtained after a booster injection (top of col. 19 and Figure 9). Morein et al disclose that the immunogenic composition is intended for immunotherapy or for the treatment of allergies, e.g., by desensitization via immunotherapy (col. 4, lines 34-53).

Morin et al do not teach specifically a method for inducing a mucosal immune response in a subject using a CpG oligonucleotide having the recited limitation.

However, at the effective filing date of the present application Krieg et al already disclose a method of stimulating immune activation by administering an isolated immunostimulatory nucleic acid sequence containing a CpG motif represented by the formula: 5'-N1X1CpGX2N2-3', wherein at least one nucleotide separates consecutive CpGs; X1 is adenine, guanine, or thymine; X2 is cytosine or thymine; N is any nucleotide and N1+N2 is from about 0-26 bases with the proviso that N1 and N2 do not

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contain a CCGG quadmer or more than one CCG or CGG trimer; and the nucleic acid sequence is from about 8-30 bases in length and wherein the immune activation effects predominantly a Th1 pattern of immune activation (see Summary of the Invention). Krieg et al further teach that the nucleic acid sequence can be administered to stimulate a subject's response to a vaccine to ameliorate disorders such as cancer, viral, fungal, bacterial or parasitic infection, specifically the nucleic acid sequence can be administered to a subject in conjunction with a particular allergen as a type of desensitization therapy to treat the occurrence of an allergic reaction associated with an asthmatic disorder (col. 6, line 63 continues to line 7 of col. 7). Infectious virus, bacteria, fungi are listed in columns 10-11. The CpG oligonucleotides are stabilized by incorporating a phosphate backbone modification, for example a phosphorothioate or phosphorodithioate modification at the 5' end or 3' end (col. 14, lines 3-32). Krieg et al also specifically teach the sequence 1826 having the sequence TCCATGACGTTCTGACGTT is a strong immune activating sequence and is a superb adjuvant, with efficacy comparable or superior to complete Freund's, but without apparent toxicity (col. 22, lines 54-62). Krieg et al further teach that the immunostimulatory nucleic acid sequence can be administered to a subject slightly before or at the same time as the vaccine, and that a conventional adjuvant (e.g., aluminum precipitates) may optionally be administered in conjunction with the vaccine, which is minimally comprised of an antigen, as the conventional adjuvant may further improve the vaccination by enhancing antigen absorption (col. 45, lines 37-46). Routes

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of administering the immunostimulatory nucleic acid include oral and transdermal and others (col. 46, lines 55-64).

Accordingly, it would have been obvious for an ordinary skilled to modify the method of Morin et al by further incorporating CpG oligonucleotides taught by Krieg et al in their immunostimulating complex for administering to a mucosal organ of a subject, particularly Morin et al. already teach that the immunostimulating complex can comprise immunostimulating agents.

An ordinary skilled artisan would have been motivated to carry out the above modification because Krieg et al already teach a CpG containing oligonucleotide having the sequence TCCATGACGTTCTGACGTT is a strong immune activating sequence and is a superb adjuvant, with efficacy comparable or superior to complete Freund's, but without apparent toxicity (col. 22, lines 54-62).

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Morin et al. and Krieg et al., coupled with a high level of skill possessed by an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

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1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 136 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 145 of copending Application No. 10/888,886. ***This is a new ground of rejection.***

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are directed to a method for inducing a mucosal immune response, comprising administering to a subject in need of a mucosal immune response an effective amount for inducing a mucosal immune response of an oligonucleotide 8-100 nucleotides in length, having a sequence including at least the following formula: 5'X1X2CGX3X4-3' wherein C is unmethylated, wherein X1, X2, X3 and X4 are nucleotides, and an antigen, wherein the antigen is not encoded in a nucleic acid vector, the oligonucleotide and the antigen are administered to the same mucosal surface of the subject, and the antigen is not a *Streptococcus pneumoniae* antigen (claim 1) and a method for inducing a mucosal immune response, comprising administering to a subject in need of a mucosal immune response an effective amount for inducing a mucosal immune response of an oligonucleotide 8-100 nucleotides in length, having a sequence including at least the following formula: 5'X1X2CGX3X4-3' wherein C is unmethylated, wherein X1, X2, X3 and X4 are nucleotides, a non-

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oligonucleotide mucosal adjuvant, and an antigen, wherein the antigen is not encoded in a nucleic acid vector, and wherein the oligonucleotide and the non-oligonucleotide mucosal adjuvant are administered to the same mucosal surface of the subject (claim 136). Claim 145 of the Co-pending application is drawn to a method for inducing IgA secretion in a subject comprising administering to a subject a composition comprising an antigen and a nucleic acid delivery complex having a CpG oligonucleotide associated with a cationic lipid or a sterol in an effective amount for inducing IgA secretion, wherein the antigen is not encoded in a nucleic acid vector, and wherein the composition is administered mucosally in the co-pending Application No. 10/691468.

The claims of the present application differ from the claim of the copending Application No. 10/888,886 in reciting specific limitation of the immunostimulatory CpG oligonucleotide and the additional administration of a non-oligonucleotide mucosal adjuvant to the subject. The claims of the present application can not be considered to be patentably distinct over claim 145 of the co-pending Application No. 10/691468 when there are specific preferred embodiments of using an immunostimulatory CpG oligonucleotide having the limitation recited by the claims of the present application (see at least pages 3-9) and the inclusion of non-oligonucleotide mucosal adjuvants in a method of inducing a mucosal immune response or IgA secretion in a subject (page 8, first full paragraph). Accordingly, claim 145 of the co-pending application falls within the scope of claims 1 and 135 of the present application.

This is because it would have been obvious to an ordinary skilled artisan to modify the method being claimed in the co-pending application by utilizing an

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immunostimulatory CpG oligonucleotide 8-100 nucleotides in length, having a sequence including at least the following formula: 5'X1X2CGX3X4-3' wherein C is unmethylated, wherein X1, X2, X3 and X4 are nucleotides and a non-oligonucleotide mucosal adjuvant that support the instant claims. An ordinary skilled artisan would have been motivated to do this because these preferred embodiments are explicitly disclosed or taught in the co-pending application.

This is a provisional obviousness-type double patenting rejection.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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